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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application	:	Kerstin Krieglstein
Application No.	:	09/786,435
Filed	:	3/20/01
For	:	USE OF TGF-BETA INHIBITORS FOR TREATING CEREBRAL DISORDERS
Examiner	:	Vanessa Ford
Attorney's Docket	:	MBP-005XX

Group Art Unit: 1645

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I hereby certify that this correspondence is being sent via facsimile to Examiner Ford, Group Art Unit 1645, Fax No. (703) 308-4242, on _____.

By: _____
Charles L. Gagnebin III
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Attorney for Applicant

* *

DECLARATION UNDER 37 CFR 1.132

I, Kerstin Krieglstein, a resident of Kopfelweg 54, D-69118 Heidelberg, Germany, hereby declare as follows:

1. I am the inventor of the above mentioned patent application.

2 I have received training in chemistry and pharmacy, having received the Prediploma degree (Chemistry) in 1983 and the M.S. degree (Pharmacy) in 1987 from the University of Munich/Germany and the Ph.D. degree in Pharmacology in 1990 from the University of Marburg/Germany.

3. I have 10 years of work experience in the development of neuronal test systems investigating the role of TGFß-like molecules in neuronal survival processes/neurodegenerative diseases such as Parkinson's disease, Morbus Alzheimer, and Amyotrophic lateral sclerosis (ALS). My work experience results from employment at various scientific institutes, e.g. postdoctoral research at the University of California, Dept. Molecular Biology and Biochemistry and at the Institute for Anatomy and Cell Biology in Marburg and Heidelberg. I obtained Habilitation in 1997 at the University of Heidelberg, received also in 1997 a Heisenberg-Stipend from the Deutsche Forschungsgemeinschaft, and became appointed Professor for Anatomy in 1999 at the University of Saarland and 2001 at the University of Goettingen. I have been the author or co-author of around 60 peer reviewed technical articles and 19 review articles relating to the role of certain members of the TGF-ß superfamily in the regulation of neuron survival and death and the development and differentiation of midbrain mesencephalic neurons. Peer recognition of my technical contribution is highlighted by receiving the 2001 „SaarLB Scientific Award" for my scientific work "Reduction of endogenous transforming growth factors ß prevents ontogenetic neuron death" (Nature Neuroscience 3, 1085-1090).

4. I understand that the Examiner for U.S Patent Application Serial No. 09/786,435 has rejected claims of this application in part because the examiner believes that the specification fails to disclose how to make and use the claimed treatment.

5. Those who would be utilizing the invention would generally be those with a high degree of skill in determining dosage and routes of administration, such as a skilled physician.

The dosages which are required to treat patients with peripheral or CNS disorders can be easily determined from such skilled persons without the requirement of undue experimentation. For example, there is a very sensitive assay available to test for TGF-ß activity: *MLEC-PAI-luciferase Assay* (Abe M, Harpel JG, Metz CN, Nunes I, Loskutoff DJ, Rifkin DB (1994): An assay for transforming growth factor-beta using cells transfected with a plasminogen activator inhibitor-1 promoter-luciferase construct. Anal Biochem 216(2):276-84). This assay is easily adaptable to any situation and has been extensively characterized and used by us and others (Abe et al., 1994; Krieglstein and Unsicker (1995): Bovine chromaffin granules contain and release a transforming growth factor-ß-like activity. J. Neurochem. 65, 1423-1426). The assay is in format, safety and practice comparable to an ELISA-assay, a typical diagnostic tool for physicians. This *MLEC-PAI-luciferase Assay* could be used to determine the amount of TGF-ß activity in the patients biopsy which allows to chose corresponding amount of TGF-ß inhibitor (dayly application of 10 µg of TGF-ß inhibitor on 10 ng TGF-ß activity). The appropriate dose of inhibitor may also be determined experimentally in this assay, by combining the patients biopsy plus varies doses of TGF-ß inhibitor to calculate the IC50. The dose for treatment can then be determined immediately by applying 10 times the IC50, multiplied by the size of the affected area as compared to the size of the biopsy.

Also general formulations of TGF-ß antibodies or antagonists which are well suitable are commonly known and

can be used without extensive experimentation. Several publications describe *in vivo* applications of such molecules with disclosure of various general formulations, e.g. Sharma K, Jin Y, Guo J, Ziyadeh FN (1996): Neutralization of TGF-beta by anti-TGF-beta antibody attenuates kidney hypertrophy and the enhanced extracellular matrix gene expression in STZ-induced diabetic mice. Diabetes 45(4):522-30; Khanna AK, Cairns VR, Becker CG, Hosenpud JD (1999): Transforming growth factor (TGF)-beta mimics and anti-TGF-beta antibody abrogates the in vivo effects of cyclosporine: demonstration of a direct role of TGF-beta in immunosuppression and nephrotoxicity of cyclosporine. Transplantation 67(6):882-9; Liu A, Dardik A, Ballermann BJ (1999): Neutralizing TGF-beta1 antibody infusion in neonatal rat delays in vivo glomerular capillary formation. Kidney Int. 56(4):1597-8.

The specific administration of neurologic agents in order to pass the blood/brain barrier and reach the brain is also topic of various published studies and granted patents and is well known from persons skilled in the art. For example, such kind of administration is discussed in detail in EP 0 504 263 "Neurologic agents for nasal administration to the brain" which has been published on June 13, 1991.

6. I declare further that all statements made herein to my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willfull false statements may jeopardize the validity of the application or any patent issuing thereon.

March 24, 2003

Date

Kerstin Krieglstein

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